ORAL IRON THERAPY IN CHILDHOOD NUTRITIONAL ANEMIA AND FACTORS AFFECTING THE OUTCOME

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the requirement

for the award of degree of

MD BRANCH – VII

PAEDIATRIC MEDICINE

INSTITUTE OF CHILD HEALTH

AND HOSPITAL FOR CHILDREN

MADRAS MEDICAL COLLEGE

CHENNAI

APRIL 2011

CERTIFICATE

This is to certify that the dissertation titled "**ORAL IRON THERAPY IN CHILDHOOD NUTRITIONAL ANEMIA AND FACTORS AFFECTING THE OUTCOME"** is a original work done by **DR. M. VENKATESAN** in the Department of Pediatrics, Institute of Child Health and Hospital For Children, Egmore, Chennai – 600 008 and has been done under our guidance and supervision during the period of his post graduate study for M.D. (Brach VII) paediatrics.

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DECLARATION

I, **DR. M. VENKATESAN** solemnly declare that the dissertation titled "**ORAL IRON THERAPY IN CHILDHOOD NUTRITIONAL ANEMIA AND FACTORS AFFECTING THE OUTCOME"** has been prepared by me.

This is submitted to **The Tamilnadu Dr. M.G.R. Medical University,** Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Examination in Pediatrics.

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SPECIAL ACKNOWLEDGEMENT

My sincere thanks to **Prof. Dr. J. Mohanasundaram M.D., Ph.D., D.N.B.,** the Dean of Madras Medical College for allowing me to do this dissertation and to utilize the facilities of this institution.

ACKNOWLEDGEMENT

I would like to explain my sincere thanks to **Prof. Dr.P. Ramachandran M.D., DCH., D.N.B, (paediatrics)** Director and superintendent (I/C), ICH & HC, for permitting me to undertake this study. I also thank him for this valuable guidance, constant encouragement and support throughout my study.

I am greatly indebted to **Prof. Dr.P.Sekar M.D.., DCH.** Medical Superintendent, Government Kilpauk Medical College Hospital, who was my former unit chief and **Prof.Dr.S.Sundari M.D., DCH.,** Professor of paediatrics, Institute of Child Health, who were a great support for me to do this study.

I would like to thank **Dr. Nedunchelian, M.D., DCH., Dr.Subramaniam M.D., DCH. Dr. Elilarasi M.D., DCH., and Dr. Karthikeyan M.D.,** for their help and support during the study.

I would like to thank all the children who participated in the study and their parents for their cooperation and support.

CONTENT

INTRODUCTION

INTRODUCTION

Nutritional deficiency disorders constitute a major health problem in India. In addition to direct implications for morbidity and mortality undernutrition predisposes children and adults to various infections[1]. Three micronutrients- vitamin A, iron, and iodine are among the most important of all the nutrients needed by the body because they are vital for developing normal learning and cognitive functions, immune defence mechanism, work capacity, and reproductive health[2]. Deficiencies of these three micronutrients are known to have devastating effects on health.

Anemia resulting from lack of sufficient iron for the synthesis of hemoglobin is the most common hematological disease of infancy and childhood .[22].1t is estimated that 30% of the global population suffers from iron deficiency anemia; most of those affected live in developing countries.[22]

Iron deficiency anemia occurs when iron absorption cannot compensate iron requirements and losses. Requirements are especially high in pregnant women, infants, Young children and adolescents. The

consequences of iron deficiency anemia are many and serious, affecting not only individual's health, but also the development of societies and countries.[3]

Global Scenario[4-7]

Iron deficiency anemia affects nearly 2 billion people around the world. Of these nearly 90% are in the developing countries.

Indian Scenario[4-7]

In India according to NFHS-3 survey, 71% of children, 32-54% of adolescent girls and 49%-58% of pregnant women are affected by iron deficiency anemia. 5.8 - 48.8% of pregnant women are severely anemic. 19% of maternal deaths are attributed to iron deficiency anemia alone.

Tamil Nadu Scenario[4-7]

In Tamil Nadu 66% of children and 42.8% of adolescent girls are affected by iron deficiency anemia. Though it is less than the national level it is definitely more than the desired level.

Strategies to prevent iron deficiency anemia

The major factors responsible for iron deficiency anemia in developing countries are reduced intake and poor bio availability of dietary iron. The iron requirements in different age groups are different.

WHO expert group[34] proposed that anemia should be considered to exist when hemoglobin is below the following levels.

Cut-off points for the diagnosis of anemia

	Gm/dl (venous blood)
Adult males	**13**
Adult females, Non-pregnant	**12**
Adult females, Pregnant	**11**
Children, 6months to 6 years	**11**
Children, 6years to 14 years	**12**

Different interventions are needed for the prevention and the control of iron deficiency. Iron fortification of staple foods or condiments directed to the whole population is a sustainable and cost-effective approach. However, at some periods of life, especially during pregnancy and in children from the age of 6 months, iron requirements are high. For

pregnant women, the current. approach favours the daily iron-folate supplementation during pregnancy but the results in terms of public health are disappointing [3].

For infants and young children, iron fortification of complementary food is effective but it is economically inaccessible to populations with limited resources. When complementary foods are not available, the preventive iron supplementation from 6 to 18 months of age has to be advised. These**,** interventions are more effective when they integrate other approaches like the improvement of the nutritional practices, infection control and the promotion of breast-feeding and when coupled with programs aiming to control other micronutrient deficiencies. The success of most interventions requires the active participation of the individuals.[3]

Information and education of the populations, especially through social mobilization campaigns, are essential because iron deficiency induces few visible symptoms, not easily recognizable by individuals. The implementation of national nutrition plans including the control of iron deficiency as one of the priorities and the participation of the public health, and education sectors, food industries; the community and the

media should contribute to the success of the interventions and to the control of iron deficiency.

The Government of India has initiated a number of Programmes in the country to improve the health and the nutritional status of the population.

National Nutritional Anemia Prophylaxis Programme[1]

To control iron deficiency anemia the National Nutritional Anemia Prophylaxis Programme (NNAPP) was launched in 1970 with the main intervention of distribution of iron and folic acid tablets to expectant mothers and children.

Ante-natal mothers were given 60 mg of iron and 500 mcg of folic acid in the 100 days of pregnancy and children were given a tablet 20 mg of elemental iron and 100 mcg folic acid.

It has been shown that NNAPP did not have the desired impact on anemia prevalence. A multicentric study by Indian Council of Medical Research revealed that 17% of pregnant women had hemoglobin levels

less than 9 gm% before iron supplementation was started and compliance rate was unsatisfactory in a considerable proportion of cases. This has been attributed to non delivery of the tablets to the women, poor quality of tablets, non consumption of tablets due lack of awareness about the importance of iron.

Side effects of oral iron therapy are also mentioned as a reason for noncompliance, but these are probably more highlighted than real. It was also noted that as high as 38% of women who had consumed the tablets regularly for more than 90 days during the last trimester had hemoglobin levels less than 10 gm% and in 20% less than 9 gm%. It was felt that 60 mg elemental iron is inadequate. So it was decided that prophylaxis programme should be converted into a control programme

National Nutritional Anemia Control Programme

The National Nutritional Anemia Control Programme was launched in 1991. Its objectives are:

1. To assess the baseline prevalence of nutritional anemia in antenatal mothers and young children through estimation of hemoglobin levels. (Now it has been decided that severe anemia should be

identified clinically as hemoglobin estimation has limited utility and there is risk of spread of diseases).

2. To put the mothers with more than 10 gm% and children with more than 8 gm% on the prophylaxis programme.

3. To monitor continuously the quality, distribution and consumption of IFA tablets.

4. To assess periodically the hemoglobin levels of the beneficiaries.

5. To motivate the beneficiary mothers to consume the tablets through relevant nutritional education and pass on the information to their children.

The target beneficiaries are 50% of total pregnant and nursing mothers 25% of total women acceptors of terminal methods and intra uterine devices and 50% of the total children between 1 and 3 years. Presently 27 million adults and 30 million child beneficiaries are covered under this programme. Also it has been made an integral part of CSSM programme. And now it is covered under RCH programme.

The recommended dosage:

Pregnant women

One big-(adult) tablet per day for 100 days, each tablet containing 100 mg of elemental iron and 500 mcg of folate and these should be provided after the first trimester of pregnancy.

Lactating women and IUD acceptors

One big tablet for 100 days.

Preschool children (1-3 years):

One small (pediatric) tablet containing 20 mg of elemental iron and 100 mcg of folic acid for 100 days every year.

Constraints of the present strategy

The recommended National Nutritional Anemia Control Programme advocating daily hematinic supplementation to pregnant women is not showing the expected results. These programmes have been ineffective, partly because side effects limit compliance, operational failures are the rule (eg, inadequate supplies and poor packaging and

presentation of supplements), and health workers and recipients lack appropriate information and motivation.[3]

The major constraints being irregular availability of hematinics and lack of education and communication of the importance of hematinic supplementation during pregnancy leading to its poor compliance among subjects[10-12].

Alternate Strategies

Strategies such as dietary diversification and food fortification have yield significant results in controlling iron deficiency anemia in developed countries. Reducing the prevalence of iron deficiency anemia in developing countries is still a matter of importance. Dietary diversification and food-based approaches pose considerable challenges before they can be implemented on a wide scale.[13]

As the programmes did not show effective results in countries such as India, the dosage of iron was increased. Gastrointestinal distress (constipation, nausea, and diarrhea) are often experienced when

consuming iron supplements, especially on an empty stomach. Therefore chronic, daily use of iron supplements in excess should be avoided.

There are a number of reports associating elevated iron stores with cardiovascular disease (CVD) and cancer. However, there are no studies that have associated specific chronic intake levels of dietary or supplemental iron with CVD and cancer. It is not possible to estimate how much iron must be consumed to result in a specific level of iron stores.

The upper limit (45 mg/day) is for the general healthy population. Individuals with hemochromatosis may not be protected by the upper limit. Relative to an adult, the normal value for hemoglobin is high in neonates, falling to lower-than-adult values by 3-6 months, and rising gradually thereafter to the adult value by the early teenage years. The role of excess iron in causing intestinal oxidative stress has drawn attention to other approaches of iron supplementation.

Prophylactic administration of iron along with antioxidants like vitamins E and C or foods rich in these vitamins is one such strategy. In

order to improve the compliance, reduce the cost of the therapy and reduce the intestinal oxidative stress schedules administering hematinics less than once daily have been tried. Gopalan C and Viteri FE in their studies have indicated that with continuous daily administration, iron absorption could decrease due to tiredness of the intestinal mucosa.

According to a study, absorption from a single dose of iron reduces from 30 -40% on the first day to as low as 3-6% after a few days of continuous daily administration. Studies carried out on pre-schoolers support that iron supplementation once or twice a week, increase their hemoglobin status significantly. The potential benefits and shortcomings of these approaches are reviewed.

In experimental animals, the absorption of supplemental iron is greatest when it is administered at times of intestinal mucosal renewal, so that each dose is received by new cell which is based on mucosal block theory. Thus, inhibition of iron absorption is minimized because of the iron overload in intestinal cells, which occurs with daily iron supplementation.

Because weekly supplementation with iron. is effective at improving iron status, this option should be thoroughly explored and evaluated in the context of programs for the prevention and the treatment of iron deficiency and anemia.

Weekly supplementation programs may improve the logistical and economic constraints that currently limit the provision of supplements to the many target population groups for whom they are recommended, but usually fail to reach. Further work is required to clarify the purpose, delivery and outcomes of iron supplementation programmes.

Technical Consultation by Human Nutrition Unitis

In India, National Family Health Survey, documented that about 74 percent children between the age of 6-35 months were anemic. A Technical Consultation was organized to discuss the Strategies for Prevention and Control of Iron Deficiency Anemia amongst under three children by the Human Nutrition Unit of the All India Institute of Medical Sciences, New Delhi on 17'h March, 2002. The consultation was sponsored by MOST-USAID Micro Nutrient Project, India.

The objectives of the consultation were: (1) to make recommendations for strengthening the child component of the National Nutritional Anemia Control Program (NNACP) and (2) to identify important researchable areas in this context.

Conclusions and Recommendations by Human Nutrition Unit

1. It is recommended that iron supplementation in the NNACP should be targeted to children in the age group of 6-35 months only.
2. Ferrous sulphate is the least expensive iron compound. It is well absorbed, has reasonably good shelf life and has few side effects at dose levels used in the NNACP.

3. The iron requirements for different ages are often defined in terms of body weight. However, in a community setting, it is not feasible to use this approach. Thus a simple fixed dose strategy rather than an exact dose based on a body weight basis is more appropriate for young children under the NNACP. With due consideration to the safety issues, it is recommended that 20 mg iron be used for anemia prophylaxis for all the children in this age group. The daily dosage of Iron Folio Acid (IFA) supplement (20 mg elemental iron + 100

mcg folic acid) recommended for children in the current on going NNACP is considered appropriate.

4. Folic acid should be added to the iron supplements to prevent folio acid deficiency anemia. More scientific data is required on the magnitude of vitamin B12 and zinc deficiencies and the benefits of adding these micronutrients before their routine supplementation in conjunction with iron can be considered as public health intervention measure under NNACP.

5. It is recommended that IFA supplementation should be done, daily for minimum of 100 days in a year.

6. The IFA supplementation should be done through the peripheral village health and the ICDS functionaries.

7. Promoting the consumption of, iron-fortified foods is an important approach to preventing anemia and this should be done wherever feasible.

A brief overview of the iron metabolism and iron deficiency anemia will help in understanding alternate strategies.

Iron Metabolism and iron deficiency Anemia

Iron deficiency anemia is the most common anemia in the world. The fourth most abundant element in the earth's crust, iron is only a trace element in biologic systems, making up only 0.004% of the body's mass. Yet it is an essential component or cofactor of numerous metabolic reactions. By weight, the great proportion of the body's iron is dedicated to its essential role as a structural component of hemoglobin.

Without sufficient iron available to the RBC precursors, normal erythropoiesis cannot take place, and anemia develops. On the other hand, iron is a toxic substance. Too much iron accumulating in vital structures (especially the heart, pancreas, and liver) produces a potentially fatal condition, hemochromatosis. Iron is an essential component of the hemoglobin molecule, without iron the marrow is unable to produce hemoglobin.

The red cell number falls and those which do reach the circulation are smaller than normal (microcytic) and lack hemoglobin, hence they are pale and under colored (hypochromic). The deficiency in iron may be absolute, that is, there is no iron available for the production of hemoglobin, this is true iron deficiency anemia. The deficiency may be

relative, that is, the iron is present in storage form in the marrow but is unavailable for hemoglobin production, and this is anemia of chronic disease.

Iron distribution

The majority of the iron is present as hemoglobin iron. Approximately 25% of the iron is maintained as storage iron (ferritin and hemosiderin) primarily in the bone marrow.

- Hemoglobin	1.5 to 3.0 gm (65 to 70%)
- Storage	
Ferritin &Hemosiderin	0.5 to 1.5 gm (20 to 30%)
-Others	
Myoglobin	
Heme enzyme	Remainder

Iron absorption

Iron absorption occurs primarily in the duodenum. Most of this iron is in the ferric form and is complexed to other organic and inorganic molecules. The acid in the stomach and hydrolytic enzymes in the small

intestine release the iron from these complexes. It is then reduced to the ferrous more readily absorbed in this state. Iron absorption is increased by the presence of glucose, some amino acids, ascorbic acid (Vitamin C).

These substances aid in the absorption process by either reducing ferric iron to the ferrous state or by helping to bind the iron to the mucosal cell receptor sites. Heme iron, iron in meat myoglobin, is more easily absorbed than elemental iron. Iron absorption is decreased by the presence of phosphate, bicarbonate, bile acids.

Once the ferrous iron (++) binds to receptors on the surface of mucosal cells, it is moved into the cell. This is an energy dependent process. in the mucosal cell the iron is oxidized back to the ferric state and bound to apoferritin in the cell. This continues until all the apoferritin bound at which point newly absorbed iron is no longer oxidized but rather is passed through the cell and into the portal circulation still in the ferrous state. In the blood, iron is bound to transferrin in the ferric state- Bound to transferrin, the iron is transported to the marrow for use or storage.

Regulation of iron absorption

The intestinal wall is covered with villi, finger-like projections, which arc covered with absorptive mucosal cells. These cells are produced in the crypts of Lieberkhun, at the base of the villi, and move upwards to the villus tip to be desquamated (lost). Each cell is produced with a set amount of apoferritin. The more iron required- by the body the less apoferritin manufactured in each cell. In other words, it is the amount of apoferritin within each mucosal cell which acts as the gatekeeper and regulates the amount of iron absorbed.

Iron transport

Transferrin is the primary iron transport protein. It is a beta globulin and is produced in liver. It has a 1/2 life of 8-11 days. Each molecule of transferrin can bind and transport two molecules of iron in the ferric (++-+) state. Transferrin prefers to carry iron to the marrow but will carry iron to other organs if the marrow is damaged or excess amounts of iron are already stored in the marrow. In rare instances when transferrin is absent (atransferrinemia) other proteins can bind iron but carry the iron to other organs such as liver, spleen and pancreas, little if any is carried to the marrow. As well as specific receptors for iron, transferrin has specific receptors for sites on the developing normoblast.

Once bound to the cell membrane, the transferrin changes shape and releases the iron. It then returns to the portal circulation to bind more iron. Under normal circumstances approximately 1-3% of the transferrin has iron bound to it.

Iron transfer across the Red Cell membrane

Iron can be transferred to developing red cells either bound to transferrin or presented as ferritin to the developing cells as they cluster around "nurse Cell" RE cells. The iron is moved into the developing red cell. Clusters of normoblast around a nurse cell are called a "feed island."

Iron Storage

Iron is stored as either ferritin or hemosiderin; ferritin consists of an outer protein shell with iron complexes within the core. The outer shell consists of 22 apoferritin molecules while the core consists of an iron phosphate complex consisting of 4,000 to 5,000 molecules of iron in each *core.* Ferritin is water soluble and a very small amount is dissolved in plasma.

The ferritin reference range for males is 15-200 ng/ml, 12 to 150 ng/ml *for* females and for children 6 months to 15 years is 7-140 mg/ml. Ferritin is not visible by light microscopy, nor is it stained by the Prussian blue reaction, Hemosiderin is aggregated ferritin molecules. The protein shell has been *altered* and as a result it is water insoluble. It can be seen by light microscopy *as* gold-brown granules and is demonstrated by the Prussian blue stain.

Daily Iron Requirements

The adult male requires approximately 1.0 mg/day, just enough to cover normal iron loss. The adult female requires approximately 2.0 mg/day, enough for daily loss and menstruation. Pregnant females require approximately 3.0 mg/day, enough for normal, on going loss and fetal requirements. Children require approximately 2.0 mg/day, enough for normal loss and extra to produce some residual iron stores and allow for increasing red cell mass.

Causes of Iron Deficiency

Failure in absorption of iron.

Increased utilization.

Pregnancy

Adolescent growth

Atransferrinemia

Failure to utilize

Lead poisoning

Chronic diseases

Blood loss

Chronic blood loss is an important cause of iron deficiency anemia particularly in older children.

Development of Iron Deficiency Anemia.

It must be remembered that anemia in iron deficiency develops slowly. The type and severity of the anemia varies with time.

Development Stages:

1. Depletion of iron stores, decreased ferritin levels, no anemia.
2. Increased transferrin levels, no anemia.
3. Fall in serum iron, no anemia.

4. Development of normocytic, normochromic anemia.
5. Development of microcytic, hypochromic anemia.

The clinical manifestations vary with the age, degree and rapidity of onset and other factors. Mild anemia is often asymptomatic. The main symptoms are exercise dyspnea, fatigue, palpitation, pica (consumption of substances such as ice, starch or clay, frequently found in iron deficiency anemia), syncope (particularly following exercise) and bounding, pulse. Dizziness, headache, syncope, tinnitus or vertigo, irritability, difficulty in sleeping or concentrating are more frequent in severe chronic anemia. Plasma ferritin level was significantly lower in children with first febrile seizure suggesting a possible role for iron insufficiency in first febrile seizures.

Common signs are pallor (color of skin, palms, oral and conjunctival mucous membrane and nail beds), tachycardia, ejection systolic murmur, mild peripheral edema and venous hums and wide pulse pressure. In old people, angina pectoris can be an important clinical manifestation.

Cardiovascular Adaptations in Anemia

The main consequence of anemia is tissue hypoxia. If anemia has developed rapidly, there may not be adequate time for compensatory adjustments to take place, so there is a sudden marked contraction of intravascular volume, resulting in postural hypotension, fall in cardiac output, shunting of blood from skin to central organs, sweating, restlessness, thirst and air hunger. If anemia occurs slowly, many adaptations occur for the oxygen maintenance, such as increasing of plasma volume and right shift of the oxygen-hemoglobin dissociation curve.

Laboratory Diagnosis of Iron Deficiency

Routine procedures

Hb, Hct and RBC count are all decreased. The degree of decrease depends upon the length of time the marrow has been without sufficient supplies of iron. It must be remembered that at any stage the red cell number will not be proportionately as low as is the Hb and Hct. This is due to the fact that the marrow can continue to produce cells which are deficient in hemoglobin.

Red Cell Distribution Width : (RDW) is increased in iron deficiency anemia.

Special procedures

A bone marrow examination is seldom, if ever, performed or needed for the diagnosis of an iron deficiency anemia. If however, a bone marrow is performed the following results would be present.

Bone Marrow

Cellularity - normal to increased.

Morphology - normoblastic with some dyserythropoiesis. Ragged reduced cytoplasm, vacuoles, multinuclearity, karyorhexis, nuclear budding, abnormal mitosis. All these may be seen but are not the predominant features of the marrow. Iron stain - absent. The absence of iron is considered to be the "gold standard" for the diagnosis of iron deficiency.

The other findings are:

Siderocytes - absent.

Serum iron - decreased.

TIBC – increased

% saturation - decreased.

Ferritin - decreased.

Free erythrocyte protoporphyrin (FEP) - increased.

Treatment

Iron supplementation is the main stay of treatment. The response is monitored with the reticulocyte count, hemoglobin and hematocrit.

Responses to iron therapy in iron deficiency anemia

Time after iron administration	Response
12-24 Hrs	Replacement of intracellular iron enzyme, subjective improvement, decrease in irritability, increase in appetite.
36-48 Hrs.	Initial bone marrow response; erythroid hyperplasia
48-72 Hrs.	Reticulocytosis, peaking at 5-7 days.
4 -30 Days	Increase in hemoglobin levels.
1 - 3 Months	Repletion of iron stores.

Iron treatment should be continued for 8 weeks after blood values are normal to replace the stores.

Failure to respond may be due to:

1. Continued bleeding
2. Failure to take iron
3. Wrong diagnosis
4. Mixed deficiency
5. Other causes – inflammation
6. Malbsorption – less likely

In 1832, ferric carbonate bills were introduced and called as Blaund's pill. Other iron formulations are ferrous sulphate, ferrous acetate, ferrous ascorbate etc.,

Recommended dosage of ferrous sulphate tablets in treatment of Iron deficiency anemia is 3 to 6 mg/kg/day.

A randomized control trial by Sachdev[13] on directly observed iron therapy in rural population in Reva district Madhya Pradesh concluded

that outcome of oral iron therapy was influenced in a majority by gastro intestinal side effects of iron therapy.

Studies propose that even with good compliance of iron supplementation, a considerable proportion of the people have not improved. A list of reasons have been proposed for the failure of oral iron supplementation. The leading causes are deficient caloric intake, associated poor nutritional status, low birth weight, gastrointestinal side effects and any intercurrent infections like recurrent pneumonia, acute gastroenteritis etc..,

When good compliance itself is a rare happening, these factors are like a hurdle in these cases. So finding out the role of these factors in the out come of oral iron therapy is important for the betterment of the children.

LITERATURE REVIEW

LITERATURE REVIEW

Despite the advances in scientific knowledge regarding various causes, treatment and various potential strategies for controlling micronutrient deficiencies, iron deficiency anemia, Vitamin A deficiency and iodine deficiency remain significant public health challenges for growing children and adolescents. Childhood anemia continues to be significant health problem and iron deficiency is the commonest nutritional cause of anemia.

While iron supplements are needed in certain groups of children and in particular regions, increased dietary calorie intake could be supplied by food fortification as well as by individual improvements in intake.

In an article published by Papagallo S, on the operational problems of an iron supplementation programme for adolescents and children by UNRWA (UNITED NATIONS RELIEF AND WORK AGENCY) he said routing iron supplementation for children and adolescents should be coupled with additional interventions like increasing dietary calories intake, improving dietary habits etc.,[14]

STUDIES REGARDING VARIOUS ASPECTS INTERFERING IN THE SUPPLEMENTATION AND ITS EFFECTIVENESS

- Thompson et al in june 2002 conducted a study at Middleton that L.B.W children had inadequate response with oral iron therapy when compared with normal birthweight in age group 1 to 10 yrs[15].

- RCT on directly observed iron therapy in rural population done in M.P. Reva district concluded that outcome of oral iron therapy was influenced in a majority by gastrointestinal side effects of oral iron therapy.

- On the role of caloric supplementation in prevention and control of iron deficiency anemia in children Madhavan Nair et al have shown that calorie supplementation is very important in the success of oral iron therapy in the treatment of iron deficiency anemia[10]. The study concluded that the children who were deprived of expected calories for that age had difficulty in improving their hemoglobin level inspite of good compliance of oral iron therapy.

- Chinese study done by Gillespie (1998) has shown that children who were given additional greens and non vegetarian diet improved well in Hemoglobin status in a randomised control trial[12].

- Buerger Nicholson et al (1997) in their study proposed that low birth weight children and preterm children, who were anemic, had difficulty in improving when compared to term , AGA children[3].

STUDY JUSTIFICATION

STUDY JUSTIFICATION

Iron deficiency anemia is the most common nutritional deficiency disorder in the country National Nutritional Anemia Control Programme covers children <36 months of age and adolescent girls. Anemia control programme covers adolescent girls for the control of anemia. All such programmes are present here for years, but anemia is still found to be a main problem in the health of the people.

Anemia has drastic ill effects on children like defects in immunity and defence mechanisms, infections, failure to thire, poor scholastic performance etc., Therefore, it has to be promptly managed.

Oral iron therapy is usually the first line management in treating iron deficiently anemia using ferrous sulphate tablets with folic acid. Ideally, the hemoglobin levels should improve by 1 to 2 months. But it has not happened regularly, as suggested by previous studies, even with a good compliance of drugs.

So, what is the cause for the failure? This study has been done with a view of finding out those factors, which are a main hurdle, in anemia

treatment and their role in causing problems at effective improvement when there is a good compliance.

Finding those factors, whether they have an impact, will help those vulnerable children to recover from anemia by management of those conditions and formulation of alternate strategies in such children.

AIM OF THE STUDY

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To study the effectiveness of oral iron therapy in childhood nutritional anemia and factors affecting the outcome, in the age group of 1 to 5 years.

MATERIALS AND METHODS

MATERIALS AND METHODS

Hypothesis of the study is that various factors play a role in outcome of oral iron therapy.

The study group involved in this study were those children who were referred to the nutrition out-patient department at Institute of child health, with hemoglobin less than 11gm % in the age group 1-5 years and with a peripheral smear showing microcytic hypochromic RBCs with anisopoikilocytosis.

The parents of the children or guardian were informed about the study and informed consent was obtained from them. This study was started in Jan 2009 and conducted upto June 2010 for a period of one and a half years.

EXCLUSION CRITERIA:

1. Lymphoreticular malignancy – blast cells in P.Smear
2. Hemolysis – increased reticulocyte count and other studies confirming hemolysis.
3. Pancytopenia, thrombocytopenia

4. Congenital heart disease / congestive cardiac failure
5. Hypersegmented WBCs, nucleated RBCs in P.smear
6. Hemoglobin < 4gm% needing blood transfusion
7. Gastritis, persistent vomiting
8. Bleeding manifestations, Jaundice
9. HIV infected children
10. Those who miss atleast 2 weeks of treatment in the 2 months of study.
11. Those who received any oral iron treatment in last 2 months / on any long term treatment.

Those who fulfilled the inclusion criteria participated in the study.

Under aseptic precautions, two ml of venous blood sample was taken from each child and sample was sent to laboratory for Hb% estimation, using cyanmethemoglobin method and reticulocyte count. EDTA (Ethylene Diamine Tetra Aceticacid) was used as anticoagulant. Peripheral blood smear was taken from each of them. Stool sample was sent to rule out any occult blood loss and worm infestation.

Each child's clinical history and examination were entered in the case proforma, which also had a questionnaire for the parents to answer, regarding various factors in the follow up visits. The results of the investigation were entered in the proforma.

Weight of the child, in kg, with a sensitivity of 100gm was recorded using standard weighting machines. Each child was weighed naked or with minimal clothing with no shoes. Weight for age, was assessed per IAP classification of malnutrition. Length of each child less than 2 years was measured using an infantometer to the nearest 0.5cm. Height of the children 2 years and above was measured using a stadiometer to the nearest 0.5cm. The child was asked to be bare footed and with chin straight along Frankfurt plane. Data were entered in proforma.

Each child at the start of the study was dewormed with a tablet of albendazole 400 mg and children less than 2 years of age were dewormed with albendazole 200mg. Then the parents were given 3mg / kg of ferrous sulphate tablets with folic acid, to be given to the child. Tablets were supplied by the Hospital for 2 weeks and they were instructed to come back after 2 weeks to collect the tablets. They were advised to give

the tablets with water, more than one hour after food and never in empty stomach.

Nutritional advice was given to increase calorie intake, if it was less than expected. Dietary advice was given to include iron rich foods.

Contact address and phone number of the principal investigator was given to the parents. At the end of the visit after 1^{st} and 2^{nd} months, the same laboratory investigations were repeated.

At each of 1^{st} and 2^{nd} visit, a predesigned questionnaire was given to the parents and was filled up by them regarding the factors expected to have an impact on the improvement of the Hb%. Results of the investigations at end of the 1^{st} visit, at end of 1^{st} and 2^{nd} month were tabulated, compared and analysed. The answers of the questionnaire were also analysed.

Daily dietary caloric intake of the child was recorded from the 24 hr recall of the parent at the end of 1^{st} and 2^{nd} month. Dietary caloric

intake as against the ICMR recommendations as expected for that age was calculated and entered.

Those who reached 11g % of Hb were considered as controls and those who did not as cases. Both groups were compared about various variables from the answered questionnaires and analysed.

ANALYSIS OF OBSERVATIONS

ANALYSIS OF OBSERVATIONS

Totally 117 children took part in this study. Out of them 101 completed the 2 months period of study. 16 of them dropped out during the study period.

Minimum age of children in this study was 1 ½ years and maximum was 5 years and the mean age was 3.4 years. 60% of the children were in the age group of 3 to 4 ½ years.

67 boys and 50 girls took part in the study. In those children, 16 boys dropped out during the study period. Totally 51 boys and 50 girls were present thoughout the study.

Only 60 children out of 101 children, had regularly consumed the tablets, daily with good compliance, as per the records perused and also on the basis of questionnaires filled by the parents. 41 children didnot take tablets daily. They had some remaining tablets regularly during the visits. Out of these 60 children who had regularly taken the iron tablets, only 51 children reached a Hb level of the 11gm % and 9 children did not.

41 children who did not consume tablets daily as per the advice, given by the investigator did not improve to reach a Hb level of 11gm %. 9 children (15%) did not improve even with a good compliance. 51 out of 60 children (85%) who took the tablets regularly improved to reach a Hb of 11gm %. These 51 children were considered as controls, and 9 children who did not improve to reach a Hb of 11gm% were considered as cases. Both groups were compared about various factors, causing the difference and the results are as follows:

51 children improved to reach a Hb level of 11 gm % they were considered as controls. 9 children did not improve and they were considered as cases.

Hb Outcome	**Tablets taken daily**	**Tablets not taken daily**	**Total**
Those achieving Hb<11 gm%	9 (15%)	41 (100%)	50
Those achieving Hb>11 gm%	51 (85%)	-	51
			101

Weight for age (% of expected)

Out of 9 cases who did not improve, 7 had grade III and IV PEM (77.7%) These children weighed less than 60% of expected for that age. 3 out of 51 controls (5.8%) had a weight of less than 60% expected for that age. 48 out of 51 controls (94.2%) weighed more than 60% expected for that age (grade I, II PEM and normal)

Hb Outcome	**Weight for age**		**Total**
	<60%	**>60%**	
Cases (Hb<11)	7 (77.2%)	2 (22.2%)	9
Controls (Hb>11)	3 (5.8%)	48 (94.2%)	51
			60

P value = 0.000 (significant)

Caloric intake:

All the children were given nutritional advice; even then some children were not given the required calories for that age, which was based on dietary assessment at the end of first and second month. All the 9 cases had <75% calorie intake expected for that age and none of them

reached the target of Hb 11gm% 4 out of 51 controls (7.8%) had <75% calorie intake expected for that age. 47 out of 51 controls (92.2%) had >75% of calorie intake expected for that age.

Hb Outcome	Calorie Intake expected for that age		Total
	<75%	>75%	
Cases (Hb<11)	9 (100%)	0 (0%)	9
Controls (Hb>11)	4 (7.8%)	47 (92.2%)	51
			60

p = 0.000 (significant)

Birth weight:

Children who were less than 2.5kg at birth were considered LBW children. 6 out of 9 cases were <2.5 kg at birth (66.6%). 7 out of 51 controls (13.7%) were less than 2.5kg at birth. 86.3% of the controls were more than 2.5kg at birth.

Hb Outcome	Birth weight (in kg)		Total
	<2.5	>2.5	
Cases (Hb<11)	6 (66.6%)	3(33.3%)	9
Controls (Hb>11)	7 (13.7%)	44(86.3%)	51
			60

p = 0.040 (significant)

ANALYSIS REGARDING TABLETS INTAKE:

Out of 51 controls, 40children(78.4%) never had the tablets in empty stomach and consumed it more than one hour after food intake. 5 out of 51 controls (9.8%) consumed the tablets in empty stomach. 6 of the 51 controls (11.8%) consumed the tablets within 1 hour of food intake.

5 out of 9 cases consumed tablet in empty stomach (55.5%) 4 out of 9 cases (44.4%) consumed the tablets within one hour of food intake

P = 0.020 (significant)

Out of 51 controls ,34 children (66.6%)did not consume tea/milk with tablets.17 out of 51 controls(33.3%)consumed tea/milk with tablets.5 out of 9 cases(55.5%) consumed tea/milk with tablets.

Hb Outcome	**Tea / Milk with tablets**		**Total**
	Yes	**No**	
Cases (Hb<11)	5 (55.5%)	4(44.4%)	9
Controls (Hb>11)	17 (33.3%)	34(66.6%)	51
			60

p = 0.000 (significant)

34 children of 51 controls(66.6%) consumed lime / curd / orange after food. All the 9 cases(100%) didnot consume.

Hb Outcome	Lime/curd/orange with food		Total
	Yes	No	
Cases (Hb<11)	0	34 (66.6)	9
Controls (Hb>11)	9(100%)	17(33.3)	51
			60

p = 0.020 (significant)

Out of 9 cases, 6 cases (66.6%) had atleast 1 episode of LRI /gastroenteritis / hospitalization. 3 cases did not have such a history. Out of 51 controls,only 11children(21.6%) had such a history.

Hb Outcome	LRI / Gastroenteritis/ hospitalisation>= 1 episode		Total
	Yes	No	
Cases (Hb<11)	6 (66.6%)	3(33.3%)	9
Controls (Hb>11)	11 (21.6%)	40(79.4%)	51
			60

P = 0.000 (significant)

None of the 51 controls and 9 cases had occult blood in stools,by stool examination. All children were dewormed at the start of study. None of the cases or controls complained of worms in stools during the study period.2 out of 51 controls and 7 out of 9 cases experienced vomiting / stomachache / constipation

All datas were tablulated and analysed by using SPSS, SAS software.

DISCUSSION

DISCUSSION

Nutritional deficiency disorder contitues a major health problem in India. In India, 74% of children have anemia according to NFHS survey. Among the micronutrients, iron is one of the most important for the body's well being.

This study has shown that there is a major setback in the compliance. About 40% of children who completed the study were not given tablets daily. There were remaining tablets at each of the visit. The reasons as derived from the questionnaires are side effects like vomiting, stomachache, constipation etc., More over, these children took the tablets in empty stomach and didnot follow the advice given at the start of study by the investigator. Parents have to be still taught more about the importance of giving the tablets regularly and as prescribed, as to avoid to ill effects of anemia and to minimize side effects of iron.

In an article published by Papagallo S, on the operational problems of iron supplementation programme for adolescents and children, by UNRWA (UNITED NATIONS RELIEF AND WORK AGENCY), he

said that iron supplementation, could be successful, when it is combined with increasing dietary caloric intake and changing dietary habits[14].

In this study also, the same thing is reflected. Among the children who had regular intake of tablets, but were taking <75% of calories expected for that age and not taking greens and vegetables in food, did not reach the target of Hb 11gm%.

Madhavan Nair et al[10], in his study titled, "Prevention and control of iron deficiency anemia in children – Role of caloric suppplementation" – proposed that caloric deprivation will be an obstacle for child who is being treated for anemia. In this study also, 9 cases who didnot improve, were taking <75% of calories as expected for that age and only 8% of controls were taking <75% of calories as expected for that age.

Thomson et al in Minesotta, U.S.A. conducted a study in 1- 10 yrs old children, who were anemic and said that birth weight was a major determinant in outcome. Low birth weight children had a difficulty in improving[15]. This study also supports the same. About 66% of the 9 cases were less than 2.5kg at birth and only 13.7% of 51 controls had a

birth weight of less than 2.5kg. Buerger Nicholson et al (1997) also made similar observation.[3]

A randomized control trial done by Sachdev[13], on directly observed iron therapy in Reva District, Madhya Pradesh concluded that the outcome was influenced by gastrointestinal side effects. In this study also, 7 out of 9 cases who did not improve, had complaints of vomiting / stomachache / constipation after tablets intake.

About 78% of the cases weighed <60% expected for that age (PEM grade III & IV. But only 5.8% of the controls weighed <60% expected for that age. It suggests that nutritional status of the child is very important in improvement of Hb status during oral iron therapy.

Intercurrent infections also may play a role in iron absorption or utilisation History of any hospitalization or loose stools or ARI was a strong factor in deciding the outcome. 40 out of 51 controls who improved, did not have any history of the same, while 6 of 9 cases has experienced the same. This suggests that frequent infections may be a factor in non-improvement despite regular iron intake.

There was no complaint of worms in stools due to prior deworming in any of the 60 children who regularly took the tablets, in the 2 months of study period.

- There was no fecal blood loss in any of the 60 children who regularly consumed the tablets daily in the 2 months of study period.
- About 33% of the controls and 55% of the cases consumed tea/milk with the tablets.
- About 35% of controls, and all 9 cases didnot consume curd/lime with food intake. About 65% of children who improved, had consumed curd/lime with food intake.

Limitations of the Study :

- The sample size is small, especially in the control group. (children who did not improve despite optimal oral iron therapy).
- Thalassemia trait, which is one of the causes for non improvement in Hb status was not determined in the study.
- Parental education or socio-economic status was not compared.

CONCLUSION

CONCLUSION

- The compliance with oral iron therapy was about 60%. 85% of the children who were totally compliant improved to reach the target hemoglobin level. 15% of the children who were totally compliant did not improve.

- The factors for non improvement in Hb status in those who were totally compliant are LBW, malnutrition, suboptimal caloric intake and frequent infections.

- Anemic children who had a low birth weight had a difficulty in improving their hemoglobin level. Children who had a normal birth weight improved well.

- One has to be more concerned about the respiratory tract infection and gastroenteritis in anemic children. Prompt treatment is needed for these conditions and counseling on diet during and after the illness is essential.

- Malnourished children (PEM 3,4) have to be still more aggressively treated for anemia along with nutritional rehabilitation. Nutritional status of the child is an important factor in improvement of anemia. Dietary advice has to be effective and one has to make sure that the child gets enough calories expected for its age.

- Consumption of greens and vegetables should be encouraged in children treated for anemia.

- It is better to avoid tea or milk after food. Curd or citrus fruits intake can be encouraged after food.

- Parents have to be counseled better about the ill effects of anemia. They have to be aware of giving the tablets daily, never in empty stomach and more than one hour after food intake. The drug compliance has to be made better and counseling has to be done to reduce the side effects.

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BIBLIOGRAPHY

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ANNEXURE I

QUESTIONNAIRE

NAME : AGE: SEX: OP/IP NO:

DATE: HEIGHT/LENGTH –

AT 1 MONTH
AT 2 MONTHS

WEIGHT:

AT 1 MONTH:
AT 2 MONTHS:

H/O AND CLINICAL ASSESSMENT:

C/O-

YES/NO

SOIL EATING –
BREATHLESSNESS-
FATIGUE-
PALPITATION-
ANOREXIA-
ICE EATING-

PAST H/O-

CONTACT WITH TB CASE-

FAMILY H/O

DEVELOPMENTAL H/O-

EXAMINATION- YES/NO

DYSMOPHIC FACIES-

PALLOR –

JAUNDICE-

LYMPHADENOPATHY-

EDEMA-

HAIR/SKIN CHANGES-

DIAGNOSIS-

INVESTIGATIONS: AT FIRST VISIT 1 MONTH 2 MONTHS

Hb%

CAC – MCV

MCHC

MCH

PCV

RDW

RBC COUNT

S.FERRITIN

PERIPHERAL SMEAR

RETICULOCYTE COUNT

FECAL OCCULT BLOOD

BIRTH WEIGHT:

BREAST FED/NOT: IF NO, WHAT MILK THEN:

WEANING AT MONTHS OF LIFE

H/O EATING SOIL/ICE ETC: YES/NO:

H/O RED COLORED STOOLS: YES/NO:

H/O WORMS IN STOOLS YES/NO: DEWORMING:

H/O LONG STAY IN HOSPITAL YES/NO:

IF YES, FOR WHAT:

H/O > 1 EPISODE PER MONTH OF LOOSE STOOLS/ ARI:

AVG USUAL DIET- AMOUNT CALORIES

MORNING

NOON

EVENING

NIGHT

WEEKLY FEED OF GREEENS : FREQ: QUANTITY

NON VEG: FREQ: QUANTITY:

DO YOU GIVE ANY OF THE FOLLOWING SOON AFTER A MEAL?

TEA

MILK

LEMON / ORANGE JUICE / CURD:

MONTH 1 2

DID YOU GIVE THE TABLETS DAILY? YES/NO:

ANY PROBLEM IN GIVING TABLETS-

WHETHER TAB WAS TAKEN IN EMPTY STOMACH:

WITHIN 1 HR OR > 1 HR OF MEAL:

TABLETS COUNT AT END OF WEEKS 2 4 6 8

H/O NO OF LOOSE STOOLS/AR1:IN LAST MONTH-

ANY HOSPITALISATION/HOSPITAL VISIT:

H/O VOMITTING/STOMACHACHE:

WHETHER ANY OF THE FOLLOWING GIVEN SOON AFTER MEAL:

TEA / MILK

LEMON/ORANGE JUICE / CURD

WHETHER GREENS / NON VEG GIVEN > THAN USUAL DIET:

ANY DEWORMING DONE:

ANNEXURE II

INFORMED CONSENT FORM

I, FATHER/MOTHER/GUARDIAN OF AGED BOY/GIRL WAS INFORMED BY THE DOCTOR THAT MY CHILD IS SUFFERING FROM ANEMIA AND THAT BLOODS SAMPLES AND STOOL TEST WILL BE TAKEN IN ASEPTIC CONDITIONS TO CONFIRM THE DIAGNOSIS.

HE TOLD ME THE CONSEQUENCES AND ILL EFFECTS OF ANEMIA. AND THAT THE INVESTIGATIONS WILLBE TAKEN AT FREE OF COST.

1, THERFORE AGREE TO GET MY CHILD PARTICIPATE IN THIS STUDY WITH MY OWN KNOWLEDGE. I WILL PROVIDE CORRECT INFORMATIONS NEEDED.

Informed consent form.

I ..... father/ mother/ guardian of the under mentioned child do hereby agree and allow my daughter/son/ward to participate in the study.

2. I confirm that I have been told about this study in my mother tongue and have had the opportunity to ask questions.
3. I confirm that i have been told about the risk and poetntial benefits for my Child's/ward's participation in this study.
4. I understand that my child's/ward's participation is voluntary and I have the right to withdraw my child/ward from this study at any part of time with out giving any reasons and with out my child's / ward's benefits being affected.
5. I agree not to restrict the use of any data or results that my arise from this study.

Name and age of the child/ward

Name and address of the father/mother/guardian

Name and address of the Witness

(prefer a person not involved in this study)

Name and address of the Investigator

ANNEXURE – III

CYANMETHEMOGLOBIN METHOD:

It is the WHO recommended method for determining Hemoglobin concentration.

Basis of the method is dilution of blood in a solution containing potassium cyanide and potassium ferricyanide. Hemoglobin, methemoglobin, Carboxy hemoglobin but not sulph Hemoglobin are converted HiCN. The absorbance of solution in then measured in spectrometer at a wavelength of 540mm or photoelectric calorimeter with a yellow green filter.

Diluents:

Drabkins cyanide ferricyanide solution with PH of 7.0- 7.4

Potassium ferricyanide	(0.607mmol/1)	200 mg
Potassium Cyanide	(0.768mmol/1)	50 mg
Potasium Dihydrogen phosphate	(1.029mmol/1)	140 mg
Non ionic detergent		1 ml
Distilled or deionized water		1 Litre

Method:

Make a 1 in 201 dilution of blood by adding 20ml blood to 4 ml of diluents. After being allowed to stand at room temperature for atleast 5 min, pour test sample to current and read absorbance in spectrometer at 540 nm or in a photoelectric calorimeter.

Advantages:

1. It allows direct comparison with HiCN standard after dilution, so batching is possible.

2. All forms of Hb,except SHb are converted to HiCN.

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Date : .....

Ref.No.Dir/EC/ICH/09 Dated: .08.09

The Institutional Review Board (Ethical Committee) of Institute of Child Health and Hospital for Children, Chennai was held on 19.12.2008 at 2.00 PM at the Deputy Superintendent's chamber.

MEMBERS PRESENT: Dr.R.Kulandai Kasthuri, Chairperson

Members:
Dr.K.Githa
Ms. Muthulakshmi (Lawyer)
Dr.P.Jeyachandran
Dr.D.Vijayasekaran
Dr.Rema Chandramohan –Secretary (Ex-officio)

Title: "A study on Oral Iron Therapy in childhood nutritional anemia and factors affecting the outcome".

The Institutional Review Board is satisfied with the amendment submitted by you on the said title. Hence the Board is pleased to approve the study.

Director and Superintendent

Director and Superintendent
Institute of Child Health and
Hospital for Children
Egmore, Chennai - 600 008

To
Dr.M.Venkatesan,
I year MD Post Graduate, M III Unit
ICH & HC
Chennai 8